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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,099	03/31/2004	Katalin Varadi	P-279.00	9454

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EXAMINER
KOSSON, ROSANNE

ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
10/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/816,099	VARADI ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-13,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-13,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on September 24, 2007 has been entered.

No claims have been amended. Claims 14-21 have been canceled. Claim 9 was canceled in a previous amendment. No claims have been added. Accordingly, claims 1-8, 10-13 and 22-23 are examined on the merits herewith.

Claim Rejections - 35 USC § 103

Claims 1-8, 10-13, 22 and 23 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Wöber et al. (US 6,124,110) in view of Hawkins et al. (US 5,625,036), Lawson et al. ("The evaluation of complex-dependent alterations in human Factor VIIa*," J Biol Chem 267(7):4834-4843, 1992), Váradi et al. ("Monitoring the bioavailability of FEIBA with a thrombin generation assay," J Thrombosis and Heamostasis 1:2374-2380, 2003), Chan (US 5,952,198), Hogan et a. (US 6,074,826), Weinstein et al. (US 6,576,422) and Dubrow et al. (US 6,756,019), and further in view of Dou et al. (US 2002/0151582) and CRC (CRC Handbook of Chemistry and Physics 51st Ed., R.C. Weast, ed., The Chemical Rubber Co., Cleveland, 1970, p. B-77). This rejection has been discussed in the previous Office actions.

Applicants assert that the claimed invention is not obvious, because the combination of the cited references not does teach or suggest a lyophilized mixture comprising $CaCl_2$ and a

fluorescently labeled thrombin substrate that forms a clear solution when dissolved in an aqueous solution. Applicants have presented new data showing that when $CaCl_2$ is added to an aqueous solution of the fluorescent substrate ZGGR-AMC, a precipitate forms. Applicants assert that, therefore, one of ordinary skill in the art would have had no expectation of success in combining the cited references to produce the claimed invention.

In reply, Applicants' data and Applicants' logic are confusing. Regarding the data, these pertain to three samples in the first experiment. The OD at 405 nm of sample 1 does not change over time. Thus, no precipitate appears to form. For all the samples in both experiments, these are 25 mg or 250 mg of ZGGR-AMC dissolved in an undisclosed volume of an aqueous buffer. Thus, the concentration is not known. An undisclosed amount of a 1M solution of $CaCl_2$ is added at an undisclosed temperature. Thus, the temperature of the mixture and the molar ratio of $CaCl_2$ to substrate are not known. Concentration, molar ratios and temperature are critical parameters in the solubility of a mixture of two solutes.

In contrast, in the assay reaction mixtures of Váradi et al., the concentration of ZGGR-AMC is less than 0.5 mM. These authors disclose that 15 mM $CaCl_2$ is added, although the volume of this solution used is not disclosed. Thus, the concentration of $CaCl_2$ is below 15 mM (see p. 2375, right col.). In the assay reaction mixtures of Lawson et al., the concentration of $CaCl_2$ is 5 mM, and the concentration of the fluorescent substrate (m-LDR-nds) is less than 1 mM (see p. 4836, right col., second and third full paragraphs). These references do not indicate that anything precipitates during any step of the assays. Because Applicants' data are not quantitative, the prior art and the new data cannot be compared in a side-to-side fashion. But, Applicants' results may be due simply to using more concentrated solutions of $CaCl_2$ and ZGGR-AMC than in the prior art. Additionally, Applicants have not performed any control experiments, that is, experiments in which solutions of $CaCl_2$ and ZGGR-AMC are lyophilized

separately, rehydrated or hydrated to form aqueous solutions, combined so that varying concentrations or amounts of one are added to the other and visa versa, and analyzed to determine which mixtures are soluble and which mixtures are not. Thus, Applicants' results are not surprising, and they may be expected.

Applicants have not explained what difference it makes whether the calcium chloride and the ZGGR-AMC (or other fluorogenic thrombin substrate) are lyophilized together or separately. That is, Applicants have not explained why the two alternatives produce different results in aqueous solution.

Regarding Applicants' arguments, if it was not known at the time of the invention that adding calcium chloride to an aqueous solution of a fluorogenic thrombin substrate, i.e., ZGGR-AMC, would produce an insoluble suspension, but the prior art teaches that the two compounds may be combined to produce a clear solution, one of ordinary skill in the art would have expected to be able to combine the two compounds to produce a clear aqueous solution. Applicants' position appears to be that one of ordinary skill in the art would not have expected this clear solution. Why would one of ordinary skill in the art have expected Applicants' new results, that the calcium chloride and ZGGR-AMC form a precipitate? If these are Applicants' results, why are the claims drawn to a kit and a method of using this kit that have the opposite results?

As previously discussed, regarding the lyophilized thrombin substrate and $CaCl_2$ preparation, Wöber et al. disclose a dry chromogenic thrombin substrate, S 2238 (Chromogenix, now Diapharma) that is soluble in water and that the thrombin reaction is initiated by the addition of $CaCl_2$ to the assay samples (see col. 5, lines 10-25). One of ordinary skill in the art would have been motivated to prepare a lyophilized reagent containing thrombin substrate and $CaCl_2$, because Hawkins et al. teach the advantages of lyophilized reagents in clinical assays.

The artisan of ordinary skill would have recognized that aqueous solutions can be lyophilized to reduce bulk and improve stability. One of ordinary skill in the art would also have recognized that the thrombin substrate and $CaCl_2$ are both soluble in water or buffer, as disclosed by Wöber et al., and they would have been combined because an enzymatic reaction may also be initiated by the addition of substrate, as well as by the addition of a catalytic substance or cofactor. In an assay of a number of samples, the enzymatic reaction is initiated by the addition of a reagent, ideally simultaneously to all samples, but this reagent may contain the substrate and the cofactor. Combining the substrate and the cofactor reduces the number of pipetting steps, thereby reducing the chance of assay errors due to pipetting errors, and reduces the number of assay steps, allowing the assay to be performed faster. Because the thrombin substrate and $CaCl_2$ are both soluble in water or buffer, one of ordinary skill in the art would have known that a solution containing both of these substances could have been prepared and lyophilized. Moreover, Hogan et al. teach that, in a diagnostic kit, or when performing an assay with a diagnostic kit, the reagents may be premixed before lyophilization so that, when reconstituted, a complete mixture is formed with the reagents in the proper ratio and ready for use (see col. 37, lines 14-29), which saves time and improves accuracy by reducing the chance for error.

As discussed previously and above, Váradi et al. and Lawson et al. disclose water-soluble fluorogenic thrombin substrates that are available in dry form. One of ordinary skill in the art at the time of the invention would have been motivated to use the thrombin substrate of Váradi et al. or Lawson et al. as the thrombin substrate in the set of reagents disclosed by Wöber et al., i.e., a fluorescent label instead of a colored label, because Váradi et al. and Lawson et al. teach that their substrates are available as dry powders that are soluble in the buffers used in a thrombin generation assay. Thus, lyophilized forms of these powders may also be prepared. One of ordinary skill in the art would have recognized that these substrates

are interchangeable with the substrate of Wöber et al., as it would have been well within his capability, when performing a thrombin generation assay, to measure the amount of fluorescence produced over time by a thrombin reaction product instead of the amount of color generated over time by a thrombin reaction product. Both fluorometric and spectrophotometric measurements are standard assay techniques. Nothing disclosed by Applicants or in the prior art indicates that lyophilizing calcium chloride and a fluorescently labeled thrombin substrate, in particular ZGGR-AMC (Applicants' substrate), together, rather than separately, changes either compound or produces a different composition when the two compounds are combined with an aqueous solvent.

In view of the foregoing, the rejection of record is maintained.

No claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR

1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rosanne Kosson
Examiner, Art Unit 1652

rk/2007-10-09

/Rebecca Prouty/
Primary Examiner
Art Unit 1652